EXPRESS MAIL NO.: EV335858279US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application of:	Morré et al.	Confirmation No.:	5585
Application No.:	09/536,551	Art Unit:	1617
Filed:	March 28, 2000	Examiner:	Wells, Lauren Q.
For:	METHODS FOR IDENTIFYING AGENTS THAT INHIBIT SERUM AGING FACTORS AND USES AND COMPOSITIONS THEREOF	Attorney Docket No.:	8951-124-999

BRIEF ON APPEAL FEE TRANSMITTAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

An original and two copies of the applicant's Brief on Appeal in the above-entitled application are submitted herewith. The item(s) checked below apply:

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	☒	Required.
	☐	Not required. (Fee paid in prior appeal.)

Please charge the required Brief filing fee to Jones Day Deposit Account No. 16-1150. A copy of this sheet is enclosed.

Respectfully submitted,

Date: January 12, 2004

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APPELLANTS' BRIEF ON APPEAL UNDER 37 C.F.R. §§ 1.191 AND 1.192

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Sir:

Pursuant to the provisions of 37 C.F.R. §§ 1.191 and 1.192, an appeal is taken herein from the final rejection of claims 12-24 of this application. Appellants submit an original and two copies of this appeal brief, accompanied by (1) a Petition for Extension of Time (in duplicate) for three months from October 12, 2003 up to and including January 12, 2004 and the appropriate fee; and (2) a Brief on Appeal Fee Transmittal Sheet (in duplicate).

I. REAL PARTY IN INTEREST

Appellants have assigned the entire right and interest in the instant application to Purdue Research Foundation, West Lafayette, Indiana.

II. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any other appeals or interferences which will directly affect, or be directly affected by, or having a bearing on the Board's decision in the present appeal.

III. STATUS OF CLAIMS

Original claims 12-24 of this application were elected for prosecution and non-elected claims 1-11 and 25-54 were withdrawn from consideration by the Examiner. Claims 12, 14, 15, and 17-24 were amended in an Amendment Under 37 C.F.R. § 1.111 filed on March 14, 2002. Claims 12-24 have been finally rejected in an Office Action mailed February 12, 2003. Claims 12, 19, 22 and 24 were further amended in a Response Under 37 C.F.R. § 1.116 with Amendment filed on August 12, 2003. A Notice of Appeal was filed on August 12, 2003 appealing the rejection of claims 12-24. Claims 12-24 are appealed.

IV. STATUS OF AMENDMENTS

Subsequent to the final rejection in the Office Action mailed February 12, 2003, Appellants submitted a Response Under 37 C.F.R. § 1.116 with Amendment on August 12, 2003 in an attempt to secure allowance of claims. For purpose of Appeal, the Amendment filed August 12, 2003 would not be entered, as indicated by the Advisory Action from the Examiner mailed August 27, 2003. A copy of the claims involved in this Appeal,

along with the proposed amendments to claims 12, 19, 22 and 24 in the Amendment filed on August 12, 2003, is presented in the Appendix.

V. SUMMARY OF THE INVENTION

The present invention, as described and claimed, relates to methods of drug screening based on finding agents that bind AR-NOX and/or modulate its activity. AR-NOX is an aging-related isoform of the cell surface NADH oxidase (NOX) protein and functions as a terminal oxidase of the plasma membrane oxido-reductase (PMOR) chain (see specification at page 5, lines 28-33). Agents identified by the claimed methods can be used to reduce the ability of AR-NOX to generate reactive oxygen species and thereby reduce oxidative stress commonly observed in aging.

The methods of the invention generally comprise first (a) incubating AR-NOX with a test agent for a time sufficient for the test agent to sequester AR-NOX; then (b) observing the outcome directly or through the use of different substrates. An "agent that sequesters AR-NOX" refers to any molecule or compound that binds, blocks, neutralizes or eliminates AR-NOX and thereby, interferes with (*e.g.*, by reducing or inhibiting) the reaction of AR-NOX with other substrates (see specification at page 8, lines 7-9). The test agent's ability to sequester AR-NOX is determined by basic biochemical binding assays (claim 12) and enzymatic assays (claims 17, 20 and 24).

VI. ISSUES

The following issue is presented for review in this appeal:

Whether claims 12-24 are not enabled for test agents under 35 U.S.C. § 112, first paragraph.

The rejected claims cover methods of screening for agents that directly bind AR-NOX (claims 12-16), methods of screening for agents that interfere with the ability of AR-NOX to reduce cytochrome c in the presence of a substrate that generates reactive oxygen species (claims 17-19), methods of screening for agents that interfere with the ability of AR-NOX to reduce a substrate such as ascorbate radical (see specification at page 14, line 16) and NAD^+ (see specification at page 14, line 19) (claims 20-23), and methods of screening for agents that interfere with the ability of AR-NOX to reduce a substrate that undergoes disulfide-thiol interchange (claim 24).

In the Office Action dated February 12, 2003, the Examiner alleged that the specification is not enabled for test agents that react with AR-NOX. In particular, the Examiner alleged that the enablement rejection is a scope of enablement rejection, because the term "test agents" encompasses every chemical possibility and NOX is present in different isoforms and hence has different chemical properties, a great amount of experimentation would be required to discover what test substances can be utilized in the claimed methods (see Office Action mailed February 12, 2003 at page 2, lines 14-15; page 2, line 22 to page 3, line 2; and page 4, lines 5-6). Instead, the Examiner suggested that the claims be limited to a Markush group of test agents disclosed in the specification (*e.g.*, cytochrome c, antibodies, ubiquinone, antisense, ribozyme molecules etc.) (see Office Action mailed February 12, 2003 at page 4, lines 10-12). In the telephonic interview of July 29, 2003, the Examiner maintained that the specification lacks enablement for test agents other than those specifically recited in the specification. Appellants respectfully disagree.

As discussed below, the Examiner's contentions are in error, and the rejection should be reversed.

VII. GROUPING OF CLAIMS

Appellants believe that with regard to the issue of patentabililty under 35 U.S.C. § 112, first paragraph, all the appealed claims stand or fall together.

VIII. ARGUMENTS

A. The Enablement Requirement And Relevant Case Law

According to applicable case law, "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." United States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The factors that are relevant in determining what constitutes undue experimentation as set forth in Wands (citing Ex parte Forman, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986)) include "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." 858 F.2d 731, 740, 8 USPQ2d 1400, 1407 (Fed. Cir. 1988). Any conclusion of nonenablement must be based on the evidence as a whole, and not based on an analysis of only one of the factors while ignoring one or more of the others. In re Wands, 858 F.2d at 740, 8 USPQ2d at 1407.

A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied; 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). The specification need only be reasonable with respect to the art involved; they need not inform the layman nor

disclose what the skilled already possess. General Electric Co. v. Brenner, 159 USPQ 335, 337 (D.C. Cir. 1968). Where a disclosure provides considerable direction and guidance on how to practice the invention and presents working examples, and where, at the time of application, the skill in the art was quite high and the methods needed to practice the invention well known, a conclusion of enablement should be made. In re Wands, 858 F.2d at 740, 8 USPQ2d at 1406.

B. The Rejected Claims And The Specification Meet The Enablement Requirement

Appellants respectfully point out that the Examiner has not made an enablement rejection over the method *as a whole*. "The invention that one skilled in the art must be enabled to make and use is *that defined by the claim(s)* of the particular application or patent." See MPEP 2164 (emphasis added). An enabling description for a process or method requires sufficient disclosure as to "how to carry out *the claimed process*." In re Barrett, 440 F.2d 1391, 1392 (CCPA 1971) (emphasis added).

Claims 12-24 recite methods of screening for agents that bind and/or interact with AR-NOX using basic biochemical binding assays or enzymatic assays. Appellants submit that the rejected claims are not directed to every possible chemical compound that bind and/or interact with NOX. Rather, claims 12-24 are directed to screening methods useful for the identification of agents that bind and/or interact with an aging-related isoform of NOX (AR-NOX) from a collection of test agents with previously unknown AR-NOX binding and/or AR-NOX interacting activities. Claims 12-24 are neither directed to test agents as compositions of matter *per se* nor directed to methods of using the agents identified by the claimed methods for other purposes.

The Examiner alleged that while screening assays are well known in the art, "testing agents" that interact with AR-NOX are not (see Office Action mailed February 12,

2003 at page 5, lines 18-20). In this statement, Appellants first point out that the Examiner seemed to admit that the manipulations involved in screening assays are well known in the art, and if so, the specification meets the enablement requirement. What seemed to concern the Examiner appeared to be the knowledge of the *results* of the claimed method where different classes of test agents are used. This is apparent in the Examiner's statement in the same paragraph (page 5, lines 16-18) that one of ordinary skill "would be forced to undergo undue experimentation to *discover* what compounds are encompassed by the term 'test agent'." (emphasis added in italics). Appellants submit that it is the purpose of the invention to use novel AR-NOX protein to select agents that interact with it and that may be developed as a therapeutic agent. To "screen" means "to select or eliminate by a selection process,"[1] and only routine experimentation is needed given the disclosures in the specification and knowledge in the art. Appellants believe that the Examiner's focus on the enablement of test agents that are selected as a result of practicing the claimed method is misplaced where the presently pending claims are directed to screening methods.

Nevertheless, Appellants submit that the specification enables the agents to be tested in the claimed methods. The term "test agent"[2] as used in the claimed methods refers to any chemical molecule or compound that one ordinarily skilled in the art would reasonably use in a screening method as described (see specification at page 8, lines 7-8). Such agents, as understood by the ordinarily skilled person, can be a drug, an antibiotic, an enzyme, a chemical compound, a mixture of chemical compounds, a member of a chemical (*e.g.*,

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[1] Merriam-Webster's Collegiate Dictionary (11th ed. 2003).

[2] An "agent", as understood by one of ordinary skill in the art, can mean "[a] force or substance that causes a change", "something that produces or is capable of producing an effect," or "a chemically, physically, or biologically active principle." See The American Heritage College Dictionary (3d ed. 1997); and Merriam-Webster's Collegiate Dictionary (11th ed. 2003).

combinatorial) library, a biological macromolecule, and analogs thereof. Examples of possible test agents described in the specification as originally filed include, but are not limited to, ubiquinone (page 1, lines 13-14; page 7, lines 11-13), antibodies (page 14, lines 4-6), those selected from a combinatorial chemistry library (page 16, lines 13-16), and proteins (page 16, lines 31-32). The term "test agent" as used in the specification and the claims is generic and should not be limited to those specifically recited in the specification. Appellants submit that the skill in the fields of biochemistry and drug screening technology is high and the number of chemical compounds that are available is abundant and growing. Many such compounds are typically organized and made available commercially in libraries. Therefore, it is unnecessary and impractical for Appellants to recite every single possible agent for testing in the claimed methods.

Appellants further submit that test agents suitable for use in the claimed methods as described in the specification are readily obtainable and even commercially available to one of ordinary skill in the art. Additionally, ubiquinone and antibodies that bind and/or interact with AR-NOX can also be prepared using a wide variety of techniques commonly known in the art. Appellants submit that one of ordinary skill in the art can purchase any one of the above-mentioned libraries, follow the steps recited in the claims and described in the specification, and determine whether a test agent in these libraries is an "agent that sequester AR-NOX" all without undue experimentation.

Not only are the test agents used in the claimed methods enabled, the method steps are also fully enabled in the specification. Claim 12 recites a method of screening for agents that bind AR-NOX by measuring the formation of a complex comprising AR-NOX and the test agent. The binding interaction between AR-NOX and the test agent can be measured in a variety of ways known in the art. For instance, the test agent may be labeled

with a radioactive isotope while AR-NOX can be immobilized on a solid phase prior to the binding reaction, and unbound labeled test agents can be removed after the binding reaction by washing the solid phase (see specification, page 15, lines 24-34). If there is a size difference between the labeled test agent and the unlabeled AR-NOX, separation can be achieved by passing the products of the binding reaction through an ultrafilter whose pores allow passage of unbound labeled test agents but not of the unbound AR-NOX or of labeled test agents bound to AR-NOX (see specification, page 16, lines 5-9).

Claims 17, 20 and 24 recite methods of screening for agents that interfere with the reaction of AR-NOX with its substrates. Specifically, claim 17 recites a method of screening for agents that affects the ability of AR-NOX to reduce cytochrome c in the presence of a substrate that generates reactive oxygen species. Cytochrome c reduction can be measured by techniques well known in the art, for example, by spectrophotometric absorbance at 540 nm to 550 nm (see specification, page 14, lines 13-14; page 24, line 36 to page 25, line 2; and claim 19).

Claim 20 recites a method of screening for agents that affect the ability of AR-NOX to reduce a substrate such as ascorbate radical (see specification at page 14, line 16) and NAD^+ (see specification at page 14, line 19). Ascorbate radical reduction and NAD^+ reduction can be measured by spectrophotometric absorbance at 265 nm and at 340 nm, respectively (see specification, page 14, lines 15-18 and claim 22; and page 8, lines 33-35 and page 24, lines 24-26, respectively).

Claim 24 recites a method of screening for agents that affect the disulfide-thiol interchange activity of AR-NOX. The disulfide-thiol interchange activity can be measured using dithio-dipyridyl substrates (see specification, page 15, lines 3-7).

Appellants submit that one skilled in the art would know how to effectively incubate a test agent with AR-NOX. The skilled person would also understand the basic principles of spectrophotometry and know how to analyze a sample's absorbance spectrum. Appellants further submit that one skilled in the art would know how to use dithio-dipyridyl substrates as taught in Morré et al., *Mol Cell Biochem.* 1999 Oct;200(1-2):7-13, which is incorporated by reference at page 15, lines 6-7 of the specification as originally filed. Based on such disclosures and knowledge in the art, no undue experimentation is required to carry out the claimed methods.

In sum, Appellants submit that the specification fully enables one of ordinary skill in the art to (i) make or obtain agents for testing in the claimed methods (*e.g.*, small molecules, chemical compounds, peptides and proteins, etc.), and (ii) carry out the biochemical binding assays and enzymatic assays of the claimed methods. Therefore, the rejection should be withdrawn.

IX. CONCLUSION

For the reasons set forth above, Appellants respectfully request that the rejection of the claims on appeal under 35 U.S.C. § 112, first paragraph, be reversed.

Respectfully submitted,

Date: January 12, 2004

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APPENDIX TO APPELLANTS' BRIEF ON APPEAL

CLAIMS ON APPEAL SHOWING PROPOSED AMENDMENT
Application No. 09/536,551
Attorney Docket No. 8951-124-999

12. (Currently Amended) A method ~~for~~ of screening for agents that sequester AR-NOX, comprising:

(a) incubating AR-NOX with a test agent for a time sufficient to allow the test agent to bind AR-NOX; and

(b) detecting the presence of a complex comprising AR-NOX and the test ~~compound~~ agent.

13. (Original) The method of claim 12 wherein the test agent is detectably labeled by a dye, an enzyme, an isotope, a fluorescent group, or a luminescent group.

14. (Previously Presented) The method of claim 12 wherein said method further comprises incubating AR-NOX with a component that is known to interact with AR-NOX.

15. (Previously Presented) The method of claim 14 wherein said component that is known to interact with AR-NOX is ubiquinone.

16. (Original) The method of claim 12 wherein the method of screening takes place within a cell.

17. (Previously Presented) A method of screening for agents that sequester AR-NOX comprising:

(a) incubating AR-NOX with a test agent, cytochrome c, and a substrate that generates reactive oxygen species, for a time sufficient for cytochrome c reduction; and

(b) detecting the presence of reduced cytochrome c, in the presence or absence of the test agent.

18. (Previously Presented) The method of claim 17 wherein the substrate that generates reactive oxygen species is superoxide dismutase.

19. (Currently Amended) The method of claim 17 wherein ~~the detection of cytochrome c is measured by~~ said detecting step comprises comparing spectrophotometric absorbance at about 540 nm to 550 nm in the presence of said test agent to the spectrophotometric absorbance at about 540 nm to 550 nm in the absence of said test agent.

20. (Previously Presented) A method of screening for agents that sequester AR-NOX comprising:

(a) incubating AR-NOX with a test agent and a substrate, wherein said substrate is reduced by AR-NOX, for a time sufficient for AR-NOX to reduce said substrate; and

(b) detecting the presence of reduced substrate in the presence or absence of the test agent.

21. (Previously Presented) The method of claim 20 wherein the substrate reduced by AR-NOX is an ascorbate radical.

22. (Currently Amended) The method of claim 21 wherein ~~the detection of ascorbate radical is measured by~~ said detecting step comprises comparing spectrophotometric absorbance at about 265 nm in the presence of said test agent to the spectrophotometric absorbance at about 265 nm in the absence of said test agent.

23. (Previously Presented) The method of claim 20 wherein the substrate reduced by AR-NOX is NAD^+.

24. (Currently Amended) A method of screening for agents that sequester AR-NOX comprising

(a) incubating AR-NOX with a test agent and a substrate, wherein said substrate undergoes disulfide-thiol interchange ~~activity~~ in the presence of AR-NOX, for a time sufficient for AR-NOX to reduce said substrate; and

(b) detecting the presence of disulfide-thiol interchange in the substrate in the presence or absence of the test agent.